Neurostructural integrity is damaged by HCV mono-infection and HIV/HCV Co-infection: A Diffusion Tensor Imaging Study

Manoj Kumar Sarma[1], Rajakumar Nagarajan[1], April Thames[2], Vanessa Streiff[3], Tim Arentsen[3], Stella Panos[4], Jason Smith[3], Charles H Hinkin[2,3], and M. Albert Thomas[1]

[1]*Radiological Sciences, UCLA School of Medicine, Los Angeles, CA, United States,* [2]*Psychiatry, UCLA School of Medicine, Los Angeles, CA, United States,* [3]*VA Greater Los Angeles Healthcare Service, Los Angeles, CA, United States,* [4]*UCLA School of Medicine, Los Angeles, CA, United States*

Introduction: Infection with the human immunodeficiency virus (HIV) and/or the Hepatitis C virus (HCV) are significant public health issues affecting millions of adults world-wide [1-4]. While the adverse effects of HIV on neurological function have been well-established, the fact that HCV infection can lead to neurological compromise has only recently been appreciated. Moreover, the additive or synergistic effects of HIV/HCV co-infection remains poorly understood as there have only been a few studies that have addressed the neuropsychological sequelae of co-infection with HIV and HCV [5], and even fewer that have explored how HIV/HCV co-infection affect white matter (WM) integrity. In this study we employed diffusion tensor imaging (DTI) to examine two markers of white matter integrity - mean diffusivity (MD), which measures the rotationally invariant magnitude of water diffusion, and fractional anisotropy (FA), an index of directional selectivity of water diffusion. Using DTI, and focusing on MD and FA, we examined the neurostructural effects of HCV mono-infection and HIV/HCV co-infection. We used an automated atlas based analysis for regional parcellation that uses Large Deformation Diffeomorphic Metric Mapping (LDDMM) for non-linear registration.

Materials and Methods: We investigated sixteen patients with HCV mono-infected (age 56.7y ± 4.9), eleven HIV/HCV co-infected (age 51y ± 9.4), and fifteen healthy controls (age 50.5y ± 10.6) who underwent MRI/MRS using 12 channel head receive coil. All subjects gave informed consent according to an institutionally approved research protocol. A Siemens 3T Trio-Tim MRI scanner (Siemens Medical Solution, Erlangen, Germany) was used and DTI was performed using a single-shot multi-section spin-echo echo-planar pulse sequence [repetition time (TR) = 10,000 ms; echo-time (TE) = 87 ms; average = 1] in the axial plane, with a 130 x 130 matrix size, 256 x 256 mm^2 field of view (FOV), 2.0 mm slice thickness, 72 slices. For each slice, diffusion gradients were applied along 64 independent orientations with b =1000 sec/mm^2 after the acquisition of b = 0 sec/mm^2 (b0) images.

DtiStudio [6] was used to calculate FA and MD. Before the normalization procedure, the skull was stripped using the b0 images and a skull-strip tool in RoiEditor software [7] using a modified version of the active contour method described by Chan and Vese [8]. A representation of the subsequent normalization process, performed using DiffeoMap [9]. The images were first normalized to the JHU-MNI-SS template using a 12-parameter affine transformation of AIR. For the non-linear transformation, dual-contrast Large Deformation Diffeomorphic Metric Mapping (LDDMM) [10] was employed. The atlas-based analysis was performed using a WM parcellation map (WMPM) [11]. Briefly, the brain was parcellated into 130 regions based on anatomical labeling, including both the gray and WM. Because of the reciprocal nature of the LDDMM, the transformation results can be used to warp the WMPM to the original MRI data, thus automatically segmenting each brain into the 130 subregions. These initial segmentation results (130 regions) were further segmented to separate the cortex and the associated peripheral WM, using the FA threshold, FA≥0.25 (Figure 1). Statistical analysis was done using analysis of covariance (ANCOVA) model with age and gender as covariate. Significance was determined with a P value of 0.05.

Results and Discussion: We found significant regional group differences in both FA and MD values. We observed statistically significant elevation of MD (Table 1) values in bilateral cerebellum, medulla and left: uncinate fasciculus, red nucleus in HCV/HIV co-infected patients compared to healthy controls. We also found statistically significant increased MD values in bilateral cerebellum, fornix/Stria terminalis and right: inferior fronto-occipital fasciculus, thalamus, medulla nucleus in HCV mono-infected patients compared to healthy controls.

We observed increase of FA in 14 regions including bilateral superior parietal lobule, postcentral gyrus, middle occipital, left fusiform gyrus, FUSIFORM GYRUS left hippocampus, right cingulate gyrus, pre-cuneus. supramarginal gyrus, posterior cotona radiata and hippocampus nucleus in HCV/HIV co-infected patients compared to healthy controls and decrease of FA in two regions: right midbrain, left red nucleus. Regional increases in FA in the HCV mono-infected patients compared to healthy controls were found in 28 regions and decrease in one region, right middle cerebellar peduncle.

Regions	Healthy Controls	HCV/HIV co-Infected		HCV mono-infected	
	Mean± SD	Mean± SD	p-value	Mean± SD	p-value
Cerebellum left	0.7366±0.037	0.950±0.107	**0.022**	0.938±0.097	**0.016**
Inferior cerebellar peduncle left	0.8505±0.020	0.953±0.063	0.061	0.979±0.080	0.056
Fornix/ Stria terminalis left	0.8772±0.017	0.914±0.027	0.164	0.927±0.013	**0.004**
Uncinate fasciculus left	0.7634±0.017	0.810±0.020	**0.040**	0.785±0.017	0.261
Red Nucleus left	0.5988±0.027	0.720±0.050	**0.014**	0.634±0.027	0.219
Medulla left	1.1178±0.093	1.597±0.280	**0.050**	1.498±0.247	0.071
Cerebellum right	0.7282±0.023	0.892±0.093	**0.037**	0.910±0.080	**0.009**
Inferior cerebellar peduncle right	0.8769±0.023	1.071±0.133	0.075	1.028±0.103	0.072
Fornix (cres) / Stria terminalis right	0.9266±0.013	0.933±0.023	0.770	0.982±0.017	**0.002**
Inferior fronto-occipital fasciculus right	0.7386±0.007	0.754±0.010	0.191	0.759±0.010	**0.028**
Thalamus right	0.8041±0.007	0.820±0.010	0.178	0.829±0.007	**0.006**
Medulla right	1.0667±0.063	1.527±0.263	**0.040**	1.444±0.213	**0.036**

Table1 1: Regional MD value ($\times 10^{-3}$ mm^2/s) changes in HCV/HIV co-infected and HCV mono-infected patients compared to healthy control. Regions significant at p <0.05 are highlighted in bold.

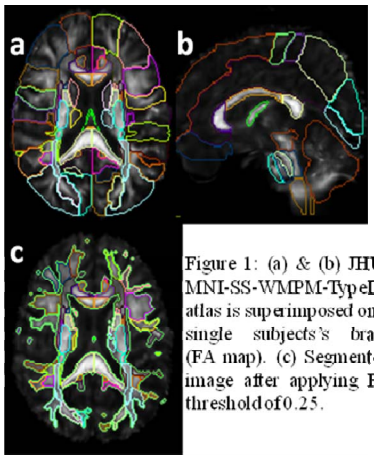

Figure 1: (a) & (b) JHU-MNI-SS-WMPM-TypeII atlas is superimposed on a single subjects's brain (FA map). (c) Segmented image after applying FA threshold of 0.25.

Conclusion: Our results showed widespread brain regions with elevation of MD and increase/decrease of FA values in both HCV/HIV co-infected and HCV mono-infected adults relative to healthy controls. These findings are consistent with previous studies [12] suggesting that HIV/HCV co-infection serves as a double assault to neuronal integrity. The decrease in WM integrity is best seen in increases in MD, a measure of generalized tissue breakdown. Indications of WM axonal integrity (FA) present a more complicated picture, with both increased and decreased FA in the HCV/HIV co-infected and HCV mono-infected patients. An interpretation of increase FA is that increased anisotropic diffusion is due to a loss of complexity of the white matter matrix in these regions. In brief, this study advances our knowledge of neurological impact of HIV/HCV co-infection, a burgeoning healthcare crisis affecting millions of people, and further established the clinical utility of DTI.

Acknowledgement: This research was supported by National Institute of Mental Health (NIMH) grants MH083553.

References: 1. Soriano V, Puoti M, Sulkowski M, et al. AIDS 2007; 21:1073-89. 2. Sherman KE, Rouster SD, Chung RT, et al. Clin Infect Dis 2002; 34:831-37. 3. Ockenga J, Tillmann HL, Trautwein C, et al. J Hepatol 1997; 27:18–24. 4. Hall C, Charlebois E, Hahn J, et al. J Gen Intern Med 2004; 19:357-65. 5. Hilsabeck RC, Castellon SA, Hinkin CH. Clin Infect Dis 2005; 4:S38-44. 6. Jiang H, van Zijl PC, Kim J, et al. Comput Methods Prog Biomed 2006; 81:106-16. 7. www.MriStudio.org. 8. Chan TF, Vese LA. IEEE Trans on Image Proc 2001; 10:266-77. 9. Faria AV, Zhang J, Oishi K, et. al. Neuroimage 2010; 52:415-28. 10. Miller MI, Beg MF, et al. Proc Natl Acad Sci USA 2005; 102:9685-90. 11. Oishi K, Faria A, Jiang H, et al.. NeuroImage 2009; 46:486-99. 12. Stebbins GT, Smith CA, Bartt RE, et al. J Acquir Immune Defic Syndr 2007; 46:564-73.